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**Review Article**

# Contribution of various factors to male infertility: a prospective review

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## ABSTRACT

Infertility is becoming a serious problem among present generation. It causes emotional instability and mental stress in affected couples. In half of the analysed cases, male factor infertility is the major contributor. Despite numerous efforts by researchers to identify various causes of male infertility, about 70 % causes remain unknown. This is due to lack of understanding of mechanisms involved in male infertility. The present review focuses on the abnormalities in male reproductive structures and contribution of endocrinological, immunological and developmental factors to male factor infertility.

**Keywords:** Male infertility, Spermatozoa, Oligospermia, Sperm count, Varicocele

## INTRODUCTION

Infertility is a significant health problem. The fertilizing potential of sperm depends on the shape of spermatozoa to perform the functions necessary for fertilizing an egg, and finally to transfer intact genetic material (DNA) to the egg at the time of fertilization.[1] Infertility in male is defined as a disease of reproductive system that impairs the body's ability to perform the basic functions of reproduction. According to the latest WHO statistics, about 50-80 million people worldwide suffer from infertility. It has been shown that male factor is solely and partially implicated in 20 to 50% of the cases of infertility.[2,3]

Furthermore, male infertility has been described as a form of infertility that is poorly responsive to primary treatment. Despite the increasing incidence and the difficulty in treating male infertility, there has been limited data available of the leading causes and risk factors of male infertility. Understanding the causes and risk factors will enable the identification of primary prevention methods as well as effective methods for the primary treatment of male infertility.

The objective of this review is to identify the causes and risk factors of male infertility which will be helpful in finding the novel approaches for prevention and primary treatment of male factor infertility.

## DICUSSION

**Table 1: Prevalence of various causes of male infertility.**

| S. no. | Etiology of male infertility | Prevalence |
|---|---|---|
| **1** | Varicocele | 35% |
| **2** | Idiopathis infertility | 25% |
| **3** | Infection of genitor urinary tract | 10% |
| **4** | Genetic | 20% |
| **5** | Endocrine | 1-5% |
| **6** | Immunological | 1-5% |
| **7** | Obstruction | 1-5% |
| **8** | Developmental | 1-5% |

In order to better understand the issues and problems associated with male infertility, we will discuss some of the key elements involved in male fertility.

### *Varicocele*

It is defined as a dilation of venous plexus that surrounds the testis. Varicocele is found in about 20-40% of infertile males, also in substantial number of fertile males. As the blood pool in vein, there is an increase in heat in the area which has detrimental effects on sperm production. Varicocele occurs more commonly as isolated left sided lesion, bilateral varicocele occurs only in 10% of cases, isolated right sided varicocele is uncommon. Varicocele can be surgically treated by removing the vein or by tying it off higher in the body.[4,5]

### *Idiopathic infertility*

It occurs when a man has an abnormal semen analysis for which no reason can be found. Now, the potential cause for idiopathic infertility is the generation of reactive oxygen species (ROS).[6,7] Hydroxyl radical (OH), superoxide anion (O2-) hydrogen peroxide (H2O2) is some of the reactive oxygen species (ROS) which cause the oxidative stress in spermatozoa. Seminal leukocytes and abnormal sperm cells are the causes of ROS generation. Controlled generation of ROS is required for fertilization, sperm capacitation and acrosome reaction. Uncontrolled generation of ROS leads to lipid peroxidation (LPO) in sperm cell membranes which ultimately causes oxidative stress. This results in damages of sperm cells and idiopathic male infertility.

### *Infection of genito-urinary tract*

Genital tract infection associated with abnormal semen quality is an isolated abnormality noted only 3-7% males. Testicular atrophy may occur following severe epididymo-orchtis with Chlamydia infection. Chlamydia can reside in the epididymis and vas deferens, affecting sperm development and fertility. The presence of anti-sperm antibodies may indicate the undiagnosed infection and estimated to be relative cause of infertility in 28-71%of infertile cases.[8,9]

## GENETIC CAUSES OF INFERTILITY

Cystic fibrosis, noonan syndrome, sex reversal syndrome, androgen receptor gene mutation, chromosomal abnormalities, chromosomal rearrangements and deletion in Y chromosome are some genetic causes of male infertility are explained below.[10]

### *Cystic fibrosis*

The main factor related to male infertility are cystic fibrosis (a gene mutation) leading to congenital absence of vas deferens. 6-10% of men with obstructive azoospermia have congenital bilateral absence of vas deferens.

### *Noonan syndrome*

An inherited condition in male which can cause abnormal gonadal (testicular) functions.[11]

### *Sex reversal syndrome*

A male who has the sex chromosomes of genetic females (XX instead of XY) resulting in azoospermia (ejaculate without sperms).

### *Androgen receptor gene mutation*

An inherited condition in which male is genetically male (46, XY), but is infertile due to defected in receptors for testosterone.

### *Chromosomal abnormalities*

Male with an extra X chromosome known as Klinefelter's syndrome, often do not produce sperm or produce very low-quality sperm.

### *Chromosomal rearrangements*

In some males, there are usual numbers of chromosomes (46) in the nucleus (centre) of the cell, but, rearrangements in the chromosomal material, where a piece of chromosome has exchange place with one another. Males with either azoospermia or oligospermia have higher frequency of chromosomal rearrangements than what is found in general population.[12]

### *Deletion in Y chromosome*

In some males, there are usual number of chromosome (46) in the body cell, but small selection of the Y chromosome (DAZ, YSRRM and AZF a,b,c deletions) are missing or deleted. Deletions in the Y chromosome is now known to result in severe oligospermia and azoospermia. These is the Y linked genes whose expression is restricted to the testes. Males carrying only micro-deleted Y chromosome will transmit the identical mutation to any son conceived by assited reproductive techniques.[13-15]

### *Endocrine causes of male infertility*

Approximately in every 90 minutes a specialized area in brain (hypothalamus) secrets GnRH (gonadotrpic hormone). GnRH signals the pituitary glands located at the base of brain to produce LH (Luteinzing hormone) and FSH (Follicle stimulating hormone). LH tells tetses to secret the male hormone testosterone. Testostreone stimulates the sexual functions and develops secondary sex characteristics (develop voice, beard). Together, testosterone and FSH stimulate testis to produce sperm (spermatogenesis).[16] In humans, testosterone and inhibin that keeps a check and balance on GnRH, LH and FSH levels. Once the Leydig cells in testicles produce enough testosterone, the hormonal system cut back on GnRH and

LH production when the Sertoli cells, which respond to FSH stimulation produce enough inhibin, the pituitary cuts back FSH production.

## HORMONAL CAUSES

There are many problems in production of hormones that stimulates spermatogenesis in testes. In case of pituitary tumors, no hormone is produced , so there is interruption in spermatogenesis.[17]

Let us discuss some male infertility problems due to overproduction or less production of hormones.

### *Hyper-prolectinema*

Over elevated production of prolactin hormone leads to Hyper-prolactinoma. This leads to reduce sperm production and suppression of FSH and LH hormones in male, ultimately cause the male infertility. Prolactin secreting tumors are suppressed by surgery or radiation therapy.

### *Hypothyroidism*

It is related with low thyroid hormone production. The main symptoms are poor semen quality, poor testicular functions, disturbance in sex drive, intolerance to cold, overweight. It can be cured by thyroid hormone replacement

### *Congenital Adrenal Hyperplasia*

In this case pituitary is suppressed by increased levels of adrenal androgens, so decrease in the level of LH and FSH hormones. The symptoms are low sperm count, increased number of immature stem cells, spermatozoa with long tapered heads, low motility. Cortisone replacement will lower the androgens and allow pituitary to function normally.

### *Hypogonadotropic-hypopituitarism*

It is mainly caused by low pituitary gland output of LH and FSH hormones thus leading to gonadotropic defects. Main symptoms include arrested sperm development, progressive loss of germ cells from testes, deterioration of semniferous tubules and leydig cells, loss of secondary sex characteristics. Testosterone supplementation can cure it effectively

### *Pan-hypopituitarism*

It is mainly caused by complete pituitary gland failure, lower GH, ACTH, TSH, LH and FSH hormones levels. Main symptoms include decreased sex drive, loss of secondary sex characteristics and undersized testicles. The infertility problem can be resolved by supplementation of missing pituitary hormones.

## IMMUNOLOGICAL CAUSES OF MALE INFERTILITY

### *Sperm antibodies (Ab)*

Antibodies produce in response to introduction of foreign material in the body as a protective mechanism. When sperm come in contact with the immune system they are recognized as foreign antigen so sperm antibodies are produced. Sperm antibodies lead to male infertility. Sperm Abs are produced due to infection present in semen.[18] Sperm antibodies may affect fertility at several stages. Abs interfere in sperm production, thus reducing sperm number in semen (oligospermia, azoospermia). Production, of sperm Abs lead to clumping /anti-agglutination of sperm, thus reducing motility. They prevent the sperm from swimming through cervical mucus, thus interfering with sperm's ability to penetrate the egg. Sperm antibodies produce disorders in sperm capacitation and acrosome reaction. Also, causes blockage of sperm ovum interaction. Abs induce sperm immunity in female. Some examples of sperm antibodies are IgG, IgA, IgM.

Blood testis barrier and tight junctions between sertoli cells play a role in keeping the developing spermatozoa and immune system separate. Blood testis barrier also suppresses the foreign antigenic expression by some testicular cells with lymphoid tissue. Immunomodulatory mechanisms within the testes eg steroids macrophages, suppressor cells, prevent activation of immune response.

## OBSTRUCTION IN REPRODUCTIVE TRACT LEADS TO SOME CAUSES OF INFERTILITY[19-21]

### *Azoospermia*

A condition in which there are no sperms in the seminal fluid.

### *Physical obstruction in the testis*

Obstruction can occur at several sites in the male reproductive anatomy. These can be further of two types.

*Obstructive azoospermia*

Generally, there is normal level of sperm production in the testes but the sperm cannot be transported to the urethera at the time of ejaculation.

*Non-obstructive azoospermia*

When dysfunction in the testis leads to such a low level of sperm production that no sperm appears in the ejaculate.

### *Retrograde ejaculation*

Sperm pass up to the urethra to bladder instead of down to urethra and out of body, which leads to azoospermia.

***Physical injury to the testes***

Testes fails to produce sperm results in azoospermia. Normal sperm concentration in various mammalian species i.e., buffalo bulls (800×106 sperm /ml), cattle bull (1000-1400×106 sperm /ml) and human (600-800×106 sperm/ml, is different. Other conditions in which lesser number of sperm is produced that lead to infertility are:

***Oligospermia***

The production of an ejaculate containing less than 20×100 sperm/ml of semen.

***Aspermia***

Failure to produce an ejaculate.

***Testospermia***

Production of an ejaculate in which more than 50% sperm are of abnormal shape

***Necrospermia***

A condition in which sperm are produced and found in semen but they are dead. These sperm cannot fertilize egg. Sperm that are not moving, are not always considered to be dead. S, special stains have to be used to make this diagnosis.

***Pyrospermia***

A condition in which the presence of white cells in semen indicates possible infection and/or inflammation.

***Hematospermia***

A condition in which blood appears in semen and can usually be seen with naked eye.

## DEVELOPMENTAL CAUSES[22]

***Cryptorchidism***

When a testis is not in its normal position in the scrotum. It may be in abdomen.

***Testicular torsion***

A condition in which the testicular twist on itself, cutting off its own blood supply.

## CONCLUSION

Male infertility is a slowly developing health problem in this century with the changes in lifestyle, food habits and developing stress in busy work schedule. This review comprehends all factors responsible for male factor infertility. In totality quality and quantity of sperm count, imbalanced hormonal levels, genetic damages, oxidative stress are the basic causes of male infertility. It is necessary to introduce new key factors and diagnostics with the advances in technology and the introduction of new methods and approaches. It is hoped that many of the causes of male infertility will soon be identified and treated.

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